[819] Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine (Vidaza®) in Patients with Myelodysplastic Syndromes (MDS). Session Type: Oral Session

Roger M. Lyons, Thomas Cosgriff, Sanjiv Modi, Heidi McIntyre, Indra Fernando, Jay Backstrom, C.L. Beach Cancer Care Centers of South Texas, San Antonio, TX, USA; Hematology and Oncology Specialists, New Orleans, LA, USA; Joliet Oncology-Hematology Associates, Ltd, Joliet, IL, USA; Pharmion Corporation, Overland Park, KS, USA

Background: Azacitidine (Vidaza®) is an effective and safe treatment (Tx) for patients (pts) with MDS (JCO 2002;20:2429) at a dosing schedule of 75 mg/m^2/day SC for 7 days every 4 weeks. A dosing schedule eliminating the need for weekend administration would be more convenient to pts and clinicians. Reported here are results of the recently completed initial Tx phase (6 cycles of randomized Tx) of an ongoing study evaluating 3 alternative azacitidine dosing schedules. Methods: In this phase II multicenter, open-label trial, MDS pts were randomized to 1 of 3 regimens administered every 4 weeks for 6 cycles: AZA 5-2-2 (75 mg/m^2/day x 5 days, followed by 2 days no Tx, followed by 75 mg/m^2/day x 2 days); AZA 5-2-5 (50 mg/m^2/day x 5 days, followed by 2 days no Tx, followed by 50 mg/m^2/day x 5 days); or AZA 5 (75 mg/m^2/day x 5 days). Major and minor hematologic improvements (HI) were assessed by International Working Group (IWG) criteria (Blood 2000;96:3671) and pts with ≥56 Tx days were IWG evaluable. To determine whether therapeutic response is maintained after 6 cycles, a 12-month maintenance phase using the AZA-5 regimen administered every 4 or 6 weeks was added, and pts with at least stable disease were eligible to participate in that phase of the study. Results: A total of 151 pts were randomized to Tx with AZA 5-2-2 (n=50), AZA 5-2-5 (n=51), or AZA 5 (n=50). Most pts are FAB classification RA/RARS (57%) or RAEB (30%). Of the 139 pts (92%) who received ≥56 days of Tx and are IWG evaluable, 74 pts (49%) completed ≥6 Tx cycles. The median number of Tx cycles across all Tx arms was 6. Of IWG-evaluable pts, 71 (51%) experienced HI (Table). The proportions of red blood cell (RBC) transfusion-dependent pts who achieved transfusion independence were AZA 5-2-2: 55% (12/22), AZA 5-2-5: 60% (12/20), and AZA-5: 67% (16/24). In FAB low-risk (RA/RARS) transfusion-dependent pts at baseline, RBC transfusion independence was reached by 60% (9/15), 56% (5/9), and 61% (11/18), respectively. No Tx-related mortality has been reported. Most grades 3 and 4 Tx-related AEs were hematological (AZA 5-2-2: 44%, AZA 5-2-5: 33%, AZA 5: 18%). Conclusions: Independent of the alternative dosing regimen, the results of the initial 6-cycle Tx phase demonstrate a consistent response for HI, RBC transfusion independence, and safety profile across a broad range of MDS pts, including FAB low-risk pts. These results appear similar to those with the approved FDA regimen and further support the benefit of azacitidine in pts who are transfusion-dependent. Eligible pts continue to receive Tx during the ongoing 12-month maintenance phase of the study.

Major Hematologic Improvement in IWG Evaluable Pts (N=139)

Major HI	AZA 5-2-2 (N=46)	AZA 5-2-5 (N=44)	AZA 5 (N=49)
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Erythroid	15 (33) (20, 48)	17 (39) (24, 55)	19 (39) (25, 54)
Platelet	10 (22) (11, 36)	8 (18) (8, 33)	9 (18) (9, 32)
Neutrophil	3 (7) (29, 100)	4 (9) (40, 100)	4 (8) (40, 100)
Any HI*	20 (44) (29, 59)	23 (52) (37, 68)	28 (57) (42, 71)

*Includes major and minor HI; pts counted only once for best response in an improvement category.

Abstract #819 appears in Blood, Volume 110, issue 11, November 16, 2007
Keywords: Hypomethylation|Regimen|Clinical Trial

Tuesday, December 11, 2007 8:00 AM

Session Info: Simultaneous Session: Myelodysplastic Syndromes: Advances in Therapeutic Options (7:30 a.m.-9:00 a.m.)

Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine in Patients With Myelodysplastic Syndromes

ABSTRACT 819

R. M. Lyons,[1] T. Cosgriff,[2] S. Modi,[3] H. McIntyre,[4] I. Fernando,[4] J. Backstrom,[4] C. L. Beach,[4]

1. Cancer Care Centers of South Texas, San Antonio, TX; 2. Hematology and Oncology Specialists, New Orleans, LA; 3. Joliet Oncology-Hematology Associates, Ltd., Joliet, IL; 4. Pharmion Corporation, Overland Park, KS

Introduction

- Although the efficacy and safety of the currently approved azacitidine 75 mg/m^2/day s.c. for 1 week every 4 weeks regimen has been established,[1] alternative dosing regimens that eliminate weekend dosing would be advantageous.
- Long-term transfusion support for patients with myelodysplastic syndromes (MDS) is costly, frequently requires specially processed blood products, and is complicated by required premedications, development of antibodies to red blood cells (RBCs), febrile or allergic reactions, and transmission of infectious agents.[2]
- Reducing transfusion dependency and normalizing cytopenias would enhance overall quality of life in patients with low- and high-risk MDS.
- Based on the mechanism of action of azacitidine, alternative dosing regimens should provide results consistent with those seen in previous studies.[1,3]

Objectives

- Assess interim response rates (RRs) associated with 3 alternative azacitidine dosing regimens using International Working Group (IWG) definitions of hematologic improvement and transfusion independence[4]
- Evaluate the interim efficacy and safety of 3 alternative azacitidine dosing regimens plus best supportive care that would eliminate the need for weekend dosing in patients with MDS

Roger Lyons is a paid consultant/Advisory Board member of Pharmion Corporation. Heidi McIntyre, Indra Fernando, Jay T. Backstrom, and C. L. Beach are employees of and have ownership interest in Pharmion Corporation. Thomas Cosgriff and Sanjiv Modi have no relevant conflicts of interest to disclose.

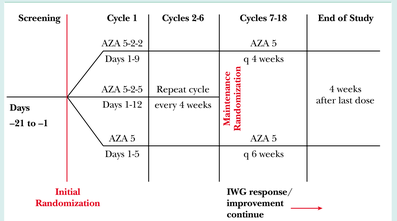
This poster includes discussion of investigational and/or unlabeled uses of drugs, including the use of alternative dosing regimens of azacitidine in myelodysplastic syndromes.

Methods

Study Design

- Multicenter, randomized, open-label, 3-arm phase II trial
- Three alternative dosing schedules, each repeated in 4-week cycles:
  - Azacitidine 75 mg/m^2/day s.c. for 5 days, then 2 days without treatment followed by azacitidine 75 mg/m^2/day s.c. for 2 days (AZA 5-2-2)
  - Azacitidine 50 mg/m^2/day s.c. for 5 days, then 2 days without treatment followed by azacitidine 50 mg/m^2/day s.c. for 5 days (AZA 5-2-5)
  - Azacitidine 75 mg/m^2/day s.c. for 5 days (AZA 5)
- After 2 cycles, the dose can be increased if the patient is not responding as defined by treatment failure or disease progression according to IWG criteria.
- After 6 cycles, patients meeting the IWG response/improvement criteria (complete response, partial response, stable disease, or hematologic improvement) were eligible to receive an additional 12 cycles.
- After a protocol amendment, the dosage regimen in the maintenance phase of the study was changed to allow randomization to receive AZA 5 either every 4 or 6 weeks

Figure 1. Study Design



Abbreviations: AZA = azacitidine; IWG = International Working Group

Response Criteria

- Hematologic improvement rates were compared among the 3 treatment arms.
- Rates of transfusion independence, defined as a transfusion-free period of ≥ 56 days in patients who were RBC-transfusion dependent or independent at baseline, were compared among the 3 treatment arms.

Evaluable Patients

- Evaluable patients were defined as those who had completed ≥ 2 treatment cycles.

Statistical Methods

- This ongoing study was designed to compare RRs with the 3 dosing regimens to those observed with standard azacitidine 75 mg/m^2/day s.c. for 1 week every 4 weeks.
- The study also compared RRs in all patients to those with low-risk MDS (refractory anemia [RA] and RA with ringed sideroblasts [RARS]) as defined by French-American-British (FAB) classification.
- No formal statistical comparisons were made for these interim data.

Results

Patient Demographics and Drug Exposure

- As of March 31, 2007, a total of 151 patients had been randomized.
- Of the patients, 36% of the patients were still on study:
  - Of the 50 patients in the AZA 5-2-2 arm, 15 (30%) were on study
  - Of the 51 patients in the AZA 5-2-5 arm, 19 (37%) were on study
  - Of the 50 patients in the AZA 5 arm, 21 (42%) were on study
- Patient demographic and disease characteristics at baseline were similar among the 3 treatment arms.
- Patients were aged 37-93 years (aged a median of 73-76 years).
- Most patients (approximately 85%) had an Eastern Cooperative Oncology Group performance status of 0/1 at baseline.
- Most patients (approximately 57%) had RA or RARS FAB subtypes.

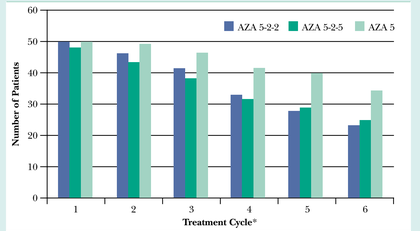
Table 1. Patient Characteristics at Baseline

	AZA 5-2-2 (n = 50)	AZA 5-2-5 (n = 51)	AZA 5 (n = 50)
Median Age (Range)	73 (37-88) years	76 (54-91) years	76 (47-93) years
Gender			
Male	28 (56%)	37 (73%)	33 (66%)
Female	22 (44%)	14 (28%)	17 (34%)
Eastern Cooperative Oncology Group Performance Status			
0	19 (38%)	14 (28%)	12 (24%)
1	23 (46%)	29 (57%)	32 (64%)
2	5 (10%)	7 (14%)	3 (6%)
3	3 (6%)	1 (2%)	3 (6%)
French-American-British Classification			
Refractory anemia	22 (44%)	21 (41%)	22 (44%)
Refractory anemia with ringed sideroblasts	7 (14%)	7 (14%)	7 (14%)
Refractory anemia with excess blasts	14 (28%)	17 (33%)	14 (28%)
Refractory anemia with excess blasts in transformation	1 (2%)	1 (2%)	2 (4%)
Chronic myelomonocytic leukemia	6 (12%)	5 (10%)	5 (10%)
World Health Organization Classification			
Refractory anemia	19 (38%)	12 (24%)	15 (30%)
Refractory anemia with ringed sideroblasts	5 (10%)	6 (12%)	8 (16%)
Refractory cytopenia with multilineage dysplasia	4 (8%)	13 (26%)	6 (12%)
Refractory cytopenia with multilineage dysplasia with ringed sideroblasts	2 (4%)	0	0
Refractory anemia with excess blasts-1	8 (16%)	10 (20%)	6 (12%)
Refractory anemia with excess blasts-2	9 (18%)	8 (16%)	10 (20%)
Myelodysplastic syndromes unknown	1 (2%)	0	1 (2%)
Myeloproliferative disorder	0	1 (2%)	0
Missing	2 (4%)	1 (2%)	4 (8%)

Abbreviation: AZA = azacitidine

- Three patients did not receive study drug, and 10 patients have completed 18 cycles.

Figure 2. Number of Cycles Received During Initial Randomization



* Each column indicates the number of patients who have completed the previous cycle and begun the next cycle.
Abbreviation: AZA = azacitidine

Hematologic Improvement

- In the interim analysis, there were 40 evaluable patients in the AZA 5-2-2 arm, 37 in the AZA 5-2-5 arm, and 45 in the AZA 5 arm.
- Interim results demonstrate promising hematologic improvement in 122 evaluable patients (53%-70%).
- Interim hematologic RRs were comparable across the 3 treatment arms.
- A bilineage response was seen in 14% of the patients (AZA 5-2-2: 13%; AZA 5-2-5: 11%; AZA 5: 18%).
- A trilineage response was seen in 5% of the patients (AZA 5-2-2: 5%; AZA 5-2-5: 5%; AZA 5: 4%).

Table 2. Hematologic Improvement

	AZA 5-2-2 (n = 40)		AZA 5-2-5 (n = 37)		AZA 5 (n = 45)	
	Number of Patients (%)	95% CI	Number of Patients (%)	95% CI	Number of Patients (%)	95% CI
Erythroid						
Major	16 (40%)	30%-61%	19 (51%)	34%-68%	18 (40%)	26%-56%
Minor	1 (3%)	0-13%	3 (8%)	2%-22%	2 (4%)	1%-15%
Platelet						
Major	9 (23%)	11%-39%	8 (22%)	10%-38%	9 (20%)	10%-35%
Minor	1 (3%)	0-13%	0	0-10%	2 (4%)	1%-15%
Neutrophil						
Major	3 (8%)	2%-20%	4 (11%)	3%-25%	7 (16%)	7%-30%
Minor	0	0-9%	0	0-10%	1 (2%)	0-12%
Overall Hematologic Improvement*	21 (53%)	34%-66%	26 (70%)	53%-84%	27 (60%)	47%-76%

* Patients with any major or minor hematologic improvement were only counted once in the overall response
Abbreviation: AZA = azacitidine

Transfusion Responses

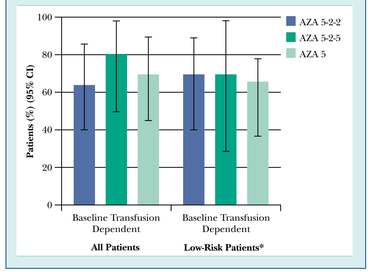
- Across the 3 treatment arms, 65%-80% of the 55 evaluable patients who were RBC-transfusion dependent at baseline achieved transfusion independence.
- Comparable beneficial effects of both RBCs and platelets on transfusions were demonstrated in all patients and in low-risk patients.

Table 3. Transfusion Independence*

	All Patients		Low-Risk Patients†	
	Number of Patients (%)	95% CI	Number of Patients (%)	95% CI
Red Blood Cell				
Dependent				
AZA 5-2-2	13/20 (65%)	41%-85%	10/14 (71%)	42%-92%
AZA 5-2-5	12/15 (80%)	52%-96%	5/7 (71%)	29%-96%
AZA 5	14/20 (70%)	46%-88%	10/15 (67%)	38%-88%
Independent				
AZA 5-2-2	12/20 (60%)	36%-81%	7/10 (70%)	35%-93%
AZA 5-2-5	19/22 (86%)	65%-97%	12/14 (86%)	58%-98%
AZA 5	19/25 (76%)	55%-91%	9/12 (75%)	43%-95%
Platelet				
Dependent				
AZA 5-2-2	2/2 (100%)	16%-100%	1/1 (100%)	3%-100%
AZA 5-2-5	0/0	–	0/0	–
AZA 5	2/2 (100%)	16%-100%	1/1 (100%)	3%-100%
Independent				
AZA 5-2-2	37/38 (97%)	86%-100%	23/23 (100%)	85%-100%
AZA 5-2-5	36/37 (97%)	86%-100%	19/21 (91%)	70%-99%
AZA 5	40/43 (93%)	81%-99%	23/26 (89%)	70%-98%

* ≥ 56 days on treatment
† By French-American-British classification
Abbreviation: AZA = azacitidine

Figure 3. Red Blood Cell Transfusion Independence



* By French-American-British classification
Abbreviation: AZA = azacitidine

Safety

- The overall profile of adverse events was generally consistent among the 3 treatment arms.
- The most commonly reported adverse events were administration site reactions/general disorders, hematologic disorders, and gastrointestinal disorders.

Table 4. Selected Grade 3/4 Adverse Events*

	AZA 5-2-2 (n = 50)	AZA 5-2-5 (n = 48)	AZA 5 (n = 50)	Total (n = 148)
≥ 1 Adverse Event	38 (78%)	34 (71%)	32 (64%)	105 (71%)
Hematologic Disorders	29 (58%)	21 (44%)	19 (38%)	69 (47%)
Anemia	11 (22%)	7 (15%)	7 (14%)	25 (17%)
Febrile neutropenia	3 (6%)	3 (6%)	1 (2%)	7 (5%)
Leukopenia	5 (10%)	4 (8%)	4 (8%)	13 (9%)
Neutropenia	20 (40%)	13 (27%)	11 (22%)	44 (30%)
Thrombocytopenia	12 (24%)	6 (13%)	7 (14%)	25 (17%)
Hemorrhagic Events	3 (6%)	2 (4%)	0	5 (3%)
Gastrointestinal	1 (2%)	0	0	1 (1%)
Rectal	0	1 (2%)	0	1 (1%)
Epistaxis	1 (2%)	0	0	1 (1%)
Infections	9 (18%)	15 (31%)	5 (10%)	29 (20%)
Candida sepsis	0	0	1 (2%)	1 (1%)
Cellulitis	2 (4%)	1 (2%)	1 (2%)	4 (3%)
Pneumonia	0	4 (8%)	1 (2%)	5 (3%)
Urinary tract infection	0	3 (6%)	1 (2%)	4 (3%)

* In patients who received ≥ 1 dose of azacitidine as of March 31, 2007
Abbreviation: AZA = azacitidine

Discussion

- In the majority of patients, hematologic improvement in individual cell lines was observed and RBC and platelet transfusion independence was established or maintained.
- Across the 3 treatment arms, there were comparable rates of transfusion independence in baseline-dependent and -independent patients in the overall evaluable patient population and in evaluable patients with FAB-defined low-risk MDS.
- These interim findings from this prospective, multicenter, randomized, controlled phase II trial indicate that the 3 alternative azacitidine dosing regimens provide comparable results, which are consistent with those previously reported with standard azacitidine 75 mg/m^2/day for 1 week every 4 weeks.[1]
- Each of the 3 alternative dosing regimens of azacitidine was tolerable, with similar safety profiles to that observed with the standard dose.

Conclusions

- Interim results suggest that the 3 alternative dosing regimens provide hematologic improvement and transfusion independence consistent with previously reported results with the standard regimen, while eliminating the need for weekend injections.
- Safety profiles of the 3 alternative dosing regimens under study are consistent with that observed with the standard dose regimen; all 3 alternative dosing schedules are generally tolerable.

References

1. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. *J Clin Oncol* 2002; 20:2429-40.
2. Gupta P, LeRoy SC, Luikart SD, et al. Long-term blood product transfusion support for patients with myelodysplastic syndromes (MDS): cost analysis and complications. *Leuk Res* 1999; 23:953-9.
3. Anthony S, Lyons R, Cosgriff T, et al. Tran[s]fusion independence assessed using three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol* 2006; 24(suppl):355s (abstract 6574).
4. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an International Working Group to standardize response criteria for myelodysplastic syndromes. *Blood* 2000; 96:3671-4.